

-126-

What is claimed is:

1. An isolated mammalian nucleic acid molecule encoding a mammalian prostate-specific membrane antigen.
5
2. An isolated mammalian DNA molecule of claim 1.
3. An isolated mammalian cDNA molecule of claim 2.
10
4. An isolated mammalian RNA molecule of claim 1.
5. An isolated mammalian nucleic acid molecule of claim 3, wherein the nucleic acid molecule is derived from humans.
15
6. A nucleic acid molecule of at least 15 nucleotides capable of specifically hybridizing with a sequence of the nucleic acid molecule of claim 1.
20
7. A DNA molecule of claim 6.
8. An RNA molecule of claim 6.
9. A nucleic acid molecule of at least 15 nucleotides capable of specifically hybridizing with a sequence of a nucleic acid molecule which is complementary to the nucleic acid molecule of claim 1.
25
10. A DNA molecule of claim 9.
30
11. An RNA molecule of claim 9.
12. A method of detecting expression of a mammalian prostate-specific membrane antigen in a cell which
35

-127-

5 comprises obtaining total mRNA from the cell, contacting the mRNA so obtained with a labelled nucleic acid molecule of claim 6 under hybridizing conditions, determining the presence of mRNA hybridized to the molecule, and thereby detecting the expression of the mammalian prostate-specific membrane antigen in the cell.

10 13. A method of detecting expression of a mammalian prostate-specific membrane antigen in tissue sections which comprises contacting the tissue sections with a labelled nucleic acid molecule of claim 6 under hybridizing conditions, determining the presence of mRNA hybridized to the molecule, 15 and thereby detecting the expression of the mammalian prostate-specific membrane antigen in tissue sections.

20 14. An isolated mammalian nucleic acid molecule of claim 2 operatively linked to a promoter of RNA transcription.

25 15. A vector which comprises the isolated mammalian nucleic acid molecule of claim 1.

16. A plasmid of claim 15.

30 17. The plasmid of claim 16 designated P55A-PSM (ATCC Accession No. 75294).

35 18. A host vector system for the production of a polypeptide having the biological activity of a mammalian prostate-specific membrane antigen which comprises the vector of claim 15 and a suitable host.

-128-

19. A host vector system of claim 18, wherein the suitable host is a bacterial cell, insect cell, or mammalian cell.
- 5 20. A method of producing a polypeptide having the biological activity of a mammalian prostate-specific membrane antigen which comprises growing the host cells of the host vector system of claim 19 under suitable conditions permitting production of the polypeptide and recovering the polypeptide so produced.
- 10 21. A mammalian cell comprising the vector of claim 15.
- 15 22. A method for determining whether a ligand can bind to a mammalian prostate-specific membrane antigen which comprises contacting a mammalian cell having an isolated DNA molecule encoding a mammalian prostate-specific membrane antigen with the ligand under conditions permitting binding of ligands to the mammalian prostate-specific membrane antigen, and determining whether the ligand binds to a mammalian prostate-specific membrane antigen.
- 20 23. A ligand detected by the method of claim 22.
- 25 24. Purified mammalian prostate-specific membrane antigen.
- 30 25. A polypeptide encoded by the isolated mammalian nucleic acid molecule of claim 1.
- 35 26. A method to identify or purify ligands of a mammalian prostate-specific membrane antigen comprising steps of:

-129-

- 5 a) coupling the purified mammalian prostate-specific membrane antigen of claim 24 to a solid matrix;
- b) incubating the coupled purified mammalian prostate-specific membrane protein derived from a) with potential ligands under the conditions permitting binding of ligands to the coupled purified mammalian prostate-specific membrane antigen to form a complex;
- 10 c) washing the ligand and coupled purified mammalian prostate-specific membrane antigen complex formed in b) to eliminate impurities; and
- 15 d) eluting the ligand from the coupled purified mammalian prostatic membrane specific antigen.
27. A ligand identified or purified by claim 26.
28. A therapeutic agent comprising a ligand of claim 23 or 27 and a cytotoxic agent conjugated thereto.
- 20 29. The therapeutic agent of claim 28, wherein the cytotoxic agent is a radioisotope or toxin.
- 25 30. A method of imaging prostate cancer in human patients which comprises administering to the patients at least one ligand of claim 27 or claim 23, capable of binding to the cell surface of the prostate cancer cell and labelled with an imaging agent under conditions permitting binding between
- 30 the ligand and the cell surface prostate-specific membrane antigen.
31. A composition comprising an effective imaging amount the ligand of claim 27 or claim 23 and a
- 35

-130-

pharmaceutically acceptable carrier.

- 5
32. A method to produce antibody using the prostate-specific membrane antigen of claims 24 or 25.
33. A method to produce monoclonal antibody using the mammalian prostate-specific membrane antigen of claims 24 or 25.
- 10 34. An antibody directed against the amino acid sequence of a mammalian prostate-specific membrane antigen.
- 15 35. An antibody directed either to peptide Asp-Glu-Leu-Lys-Ala-Glu (SEQ ID No. 39), or Asn-Glu-Asp-Gly-Asn-Glu (SEQ ID No. 40) or Lys-Ser-Pro-Asp-Glu-Gly (SEQ ID No. 41) of the prostate-specific membrane antigen.
- 20 36. A monoclonal antibody of claim 34 or 35.
37. A therapeutic agent comprising an antibody of claim 34 or 35 and a cytotoxic agent conjugated thereto.
- 25 38. A therapeutic agent of claim 34 or 35, wherein the cytotoxic agent is either a radioisotope or toxin.
- 30 39. A method of imaging prostate cancer in human patient which comprises administering to the patient at least one antibody of claim 34 or 35 capable of binding to the cell surface of the prostate cancer cell and labeled with an imaging agent under conditions permitting formation of a complex between the monoclonal antibody and the
- 35 cell surface prostate-specific membrane antigen.

-131-

- 5 40. An imaging method of claim 39 wherein multiple antibodies directed against the amino acid sequence of a mammalian prostate-specific membrane antigen, binding to different epitopes and not interfering with the binding of each other, are administered to the patient.
- 10 41. A method of claim 39, wherein the imaging agent is a radioisotope.
- 15 42. A prostate cancer specific imaging agent comprising the antibody of claim 34 or 35 and a radioisotope conjugated thereto.
43. A composition comprising an effective imaging amount of the antibody of claim 34 or 35 and a pharmaceutically acceptable carrier.
- 20 44. An immunoassay for measuring the amount of a mammalian prostate-specific membrane antigen in a biological sample comprising steps of:
- 25 a) contacting the biological sample with at least one antibody of claim 34 or 35 to form a complex with said antibody and the mammalian prostate-specific membrane antigen, and
- b) measuring the amount of the prostate-specific membrane antigen in said biological sample by measuring the amount of said complex.
- 30 45. An immunoassay for measuring the amount of a mammalian prostate-specific membrane antigen in a biological sample comprising steps of:
- 35 a) contacting the biological sample with at least one ligand of claim 23 or 27 to form a complex with

-132-

said ligand and the mammalian prostate-specific membrane antigen, and

b) measuring the amount of the mammalian prostate-specific membrane antigen in said biological sample by measuring the amount of said complex.

46. A method to purify mammalian prostate-specific membrane antigen comprising steps of:

a) coupling at least one antibody of claim 34 or 35 to a solid matrix;

b) incubating the coupled antibody of a) with a cell lysate containing prostate-specific membrane antigen under the condition permitting binding of the coupled antibody and prostate-specific membrane antigen;

c) washing the solid matrix to eliminate impurities and

d) eluting the prostate-specific membrane antigen from the coupled antibody.

47. A transgenic nonhuman mammal which comprises the isolated nucleic acid molecule of claim 1.

48. A transgenic nonhuman mammal whose genome comprises antisense DNA complementary to DNA encoding a mammalian prostate-specific membrane antigen so placed as to be transcribed into antisense mRNA complementary to mRNA encoding the prostate-specific membrane antigen and which hybridizes to mRNA encoding the mammalian prostate-specific membrane antigen thereby reducing its translation.

49. A method of suppressing or modulating metastatic ability of prostate tumor cells, prostate tumor growth or elimination of prostate tumor cells,

-133-

comprising introducing a DNA molecule encoding a prostate specific membrane antigen operatively linked to a 5' regulatory element into a tumor cell of a subject, in a way that expression of the prostate specific membrane antigen is under the control of the regulatory element, thereby suppressing or modulating metastatic ability of prostate tumor cells, prostate tumor growth or elimination of prostate tumor cells.

50. The method of claim 49, wherein the DNA molecule encoding prostate specific membrane antigen operatively linked to a 5' regulatory element forms part of a transfer vector which is inserted into a cell or organism, and which vector is capable of replication and expression of prostate specific membrane antigen.
51. The method of claim 50, wherein the DNA molecule encoding prostate specific membrane antigen is integrated into a genome of a eukaryotic or prokaryotic cell.
52. The method of claim 51, wherein a host cell contains and/or expresses a prostate specific membrane antigen.
53. The method of claim 49, wherein the DNA molecule encoding prostate specific membrane antigen is introduced by a delivery vehicle.
54. The method of claim 53, wherein the delivery vehicle is bacterial, viral, fungal, animal, or liposomal.

-134-

55. The method of claim 49, wherein the 5' regulatory element is a promoter.
56. The method of claim 49, wherein the 5' regulatory element is an enhancer.
57. The method of claim 49, wherein the subject is a mammal.
58. The method of claim 57, wherein the subject is a human.
59. A method of suppressing or modulating metastatic ability of prostate tumor cells, prostate tumor growth or elimination of prostate tumor cells, comprising introducing a DNA molecule encoding a prostate specific membrane antigen operatively linked to a 5' regulatory element coupled with a therapeutic DNA into a tumor cell of a subject, thereby suppressing or modulating metastatic ability of prostate tumor cells, prostate tumor growth or elimination of prostate tumor cells.
60. The method of claim 59, wherein the DNA molecule encoding prostate specific membrane antigen operatively linked to a 5' regulatory element forms part of a transfer vector which is inserted into a cell or organism, and which vector is capable of replication and expression of prostate specific membrane antigen.
61. The method of claim 60, wherein the DNA molecule encoding prostate specific membrane antigen is integrated into a genome of a eukaryotic or prokaryotic cell.

-135-

62. The method of claim 61, wherein a host cell contains and/or expresses a prostate specific membrane antigen.

5 63. The method of claim 59, wherein the DNA molecule encoding prostate specific membrane antigen is introduced by a delivery vehicle.

10 64. The method of claim 63, wherein the delivery vehicle is bacterial, viral, fungal, animal, or liposomal.

15 65. The method of claim 59, wherein the 5' regulatory element is a promoter.

66. The method of claim 59, wherein the 5' regulatory element is an enhancer.

20 67. The method of claim 59, wherein the therapeutic DNA encodes a cytokine, viral antigen, or a pro-drug activating enzyme.

25 68. The method of claim 67, wherein the cytokine is interleukin-2.

69. The method of claim 67, wherein the cytokine is interleukin-12.

30 70. The method of claim 67, wherein the cytokine is interferon.

35 71. The method of claim 67, wherein the cytokine is granulocytic macrophage - colony stimulating factor.

-136-

72. The method of claim 59, wherein the subject is a mammal.
73. The method of claim 72, wherein the subject is a human.
74. A prostate tumor cell, comprising a DNA molecule of claim 2 under the control of a prostate specific membrane antigen operatively linked to a 5' regulatory element.
75. The method of claim 74, wherein the 5' regulatory element is a promoter.
76. The method of claim 74, wherein the 5' regulatory element is an enhancer.
77. A therapeutic vaccine for preventing human prostate tumor growth or stimulation of prostate tumor cells in a subject, comprising administering an effective amount to the prostate cell of claim 74, and a pharmaceutical acceptable carrier, thereby preventing the tumor growth or stimulation of tumor cells in the subject.
78. A method of detecting hematogenous micrometastatic tumor cells of a subject, comprising (A) performing nested polymerase chain reaction (PCR) on blood, bone marrow or lymph node samples of the subject using the prostate specific membrane antigen primers, and (B) verifying micrometastases by DNA sequencing and Southern analysis, thereby detecting hematogenous micrometastatic tumor cells of the subject.

-137-

79. The method of claim 78, wherein the primers are derived from prostate specific antigen.

5 80. The method of claim 78, wherein the subjects is administered hormones in an effective amount.

81. The method of claim 80, wherein the hormone is an androgen suppressor.

10 82. The method of claim 78, wherein the subject is a mammal.

83. The method of claim 82, wherein the subject is a human.

15 84. A method of abrogating mitogenic response due to transferrin, comprising introducing a DNA molecule encoding prostate specific membrane antigen operatively linked to a 5' regulatory element into
20 a tumor cell, the expression of which gene is directly associated with a defined pathological effect within a multicellular organism, thereby abrogating mitogen response due to transferrin.

25 85. The method of claim 84, wherein the 5' regulatory element is a promoter.

86. The method of claim 84, wherein the 5' regulatory element is an enhancer.

30 87. The method of claim 84, wherein the DNA molecule encoding prostate specific membrane antigen operatively linked to a 5' regulatory element forms part of a transfer vector which is inserted into a
35 cell or organism, and which vector is capable of

-138-

replication and expression of prostate specific membrane antigen.

5 88. The method of claim 84, wherein the DNA molecule encoding prostate specific membrane antigen is integrated into a genome of a eukaryotic or prokaryotic cell.

10 89. The method of claim 88, wherein a host cell contains and/or expresses a prostate specific membrane antigen.

add D8 >